UNITED STATES DISTRICT COURT
DISTRICT OF MASSACHUSETTS

ASTELLAS INSTITUTE FOR REGENERATIVE MEDICINE,	*	
Plaintiff,	*	
v.	*	Civil Action No. 17-cv-12239-ADB
IMSTEM BIOTECHNOLOGY, INC., et al.,	*	
Defendants.	*	

FINDINGS OF FACT AND CONCLUSIONS OF LAW

Table of Contents

BURROUGHS, D.J.

I. INTRODUCTION

Plaintiff Astellas Institute for Regenerative Medicine ("Astellas") brings this action against Defendants ImStem Biotechnology, Inc. ("ImStem"), Dr. Xiaofang Wang, and Dr. Ren-He Xu (collectively, "Defendants"), alleging claims for correction of inventorship of a patent under 35 U.S.C. § 256 and unfair trade practices under Massachusetts General Laws Chapter 93A. [ECF No. 113]. Defendants bring counterclaims for correction of inventorship of two patents under 35 U.S.C. § 256. [ECF No. 91].

II. PROCEDURAL HISTORY

On November 13, 2017, Astellas filed suit against Defendants, seeking a correction of inventorship on Patent No. 9,745,551 ("the '551 Patent") and other state-law remedies. [ECF No. 1]. On January 10, 2018, Defendants filed their answer and counterclaims, including claims for correction of inventorship on Patent No. 8,961,956 ("the '956 Patent") and unjust enrichment. [ECF No. 20]. On January 31, 2018, Astellas filed a motion to dismiss the counterclaims, [ECF No. 21], which the Court denied on September 28, 2018, [ECF No. 37]. Defendants then filed an amended answer and counterclaim complaint on August 28, 2019, which added a claim for correction of inventorship on Patent No. 8,962,321 ("the '321 Patent"), [ECF No. 91], and Astellas answered the counterclaims on September 6, 2019, [ECF No. 92]. On October 3, 2019, Astellas filed an amended complaint, [ECF No. 113], and Defendants filed a second amended answer on October 17, 2019. [ECF No. 114].

The parties filed motions for partial summary judgment on December 19, 2019, [ECF Nos. 127, 131], and the Court entered its Order on the motions on March 4, 2020, [ECF No. 163]. The Court granted summary judgment on Astellas' claim to add Drs. Erin Kimbrel and Robert Lanza to the '551 patent and also granted its request to limit Defendants' recovery on

their unjust enrichment claim to equitable relief only. [Id.]. The Court otherwise denied the motions. [Id.].

The case proceeded to trial on Counts I (correction of inventorship, 35 U.S.C. § 256) and V (violation of Mass. Gen. Laws ch. 93A), and on Counterclaim Counts I and II (correction of inventorship, 35 U.S.C. § 256).[1] From November 2 through November 16, 2020, the Court heard testimony from five fact witnesses and six expert witnesses. [ECF Nos. 238–42, 249–53]. The Court heard closing arguments on November 17, 2020, [ECF No. 254], and the parties later submitted proposed findings of fact and conclusions of law, [ECF Nos. 243, 245, 246, 247-1].

Having considered the evidence presented at trial and the parties' post-trial submissions, the Court makes the following findings of fact and conclusions of law pursuant to Federal Rule of Civil Procedure 52(a).

III. FINDINGS OF FACT[2]

A. Overview of Regenerative Medicine

The inventions at issue in this case arise from the field of regenerative medicine, which seeks to harness the body's own ability to heal itself using stem cells. [Nov. 4 Tr. at 11:15–21]. Mesenchymal stem cells ("MSCs") are undifferentiated cells that have the capacity to differentiate into cells that can eventually form organs, blood, tissue, bone, and muscle. [Id. at 19:2–15; Nov. 5 Tr. at 17–18].[3] There are several potential benefits to using MSCs

[1] In its pretrial brief, Astellas dropped its negligent misrepresentation, misappropriation of trade secrets, and breach of contract claims. [ECF No. 218]. During its opening statement, Astellas stated that it was also dropping its conversion and unjust enrichment claims. [ECF No. 238; Nov. 2 Tr. at 43:6–9]. Defendants also dropped their unjust enrichment counterclaim. [ECF No. 247-1 at 9].

[2] The parties have stipulated to certain facts, [ECF No. 218-1]; those facts are referenced throughout this Section.

[3] MSCs are sometimes referred to as mesenchymal stromal cells. [Nov. 2 Tr. at 99:14–22].

therapeutically. First, MSCs can increasingly be manipulated to follow a set path, for example to perhaps one day differentiate into a specific organ, which could facilitate organ transplantation without donors. [Nov. 2 Tr. at 86:15–18; Nov. 4 Tr. at 19:5–13]. Second, MSCs can be grown in a lab, allowing for an unlimited supply. [Nov. 2 Tr. at 95:10–15]. Third, tissues and organs grown through MSCs will avoid the problem of rejection caused by transplanting donor tissue and organs, as stem cells grown in the lab can be transplanted into anyone. [Id. at 86:15–19; Nov. 4 Tr. at 35:15–18]. Various trophic factors, including chemokines and cytokines (proteins), which are secreted by the cells, give MSCs the power to regenerate and repair the body. [Nov. 4 Tr. at 20:4–12, 58:13–22]. These secretions stop T cells (immune cells that cause inflammation) from proliferating and attract existing stem cells, giving MSCs significant clinical potential. [Id. at 33:14–17, 57:22–58:3, 58:13–22; Nov. 10 Tr. at 129:21–24].

MSCs can be derived from several sources, including bone marrow, embryos, umbilical cords, and adipose (fat) cells. [Nov. 4 Tr. at 85:15–24; Nov. 5 Tr. at 27:10–19]. While all of these sources can be used to create MSCs, the properties of the MSCs derived from each can vary slightly. [Nov. 3 Tr. at 96:24–97:9; Nov. 10 Tr. at 38:13–16, 38:18–39:3]. For example, bone marrow-derived MSCs ("BM-MSCs"), which are created using bone marrow from an adult body, tend to be less potent, whereas MSCs derived from embryonic stem cells ("ESCs") are younger and more potent. [Nov. 2 Tr. at 117:2–9].

B. Astellas and Drs. Kimbrel and Lanza

Astellas is the successor in interest to Advanced Cell Technology, Inc. ("ACT"), Ocata Therapeutics, Inc., and Stem Cell & Regenerative Medicine International, Inc. ("SCRMI").

[ECF No. 218-1 ¶ 2].[4] Dr. Lanza is Astellas' Chief Scientific Officer. [Nov. 2 Tr. at 78:16–19]. In 1999, he joined ACT to work on human therapies. [Id. at 85:4–5, 89:25–90:1]. He brought his experience working with stem cells and autoimmune therapies, which he had developed through previous academic and industry positions. [Id. at 84:10–86:1]. Dr. Kimbrel is Astellas' Executive Director for Regenerative Medicine. [Nov. 3 Tr. at 4:21–22]. In 2009, she started working at SCRMI, which was a joint venture between ACT and another biotechnology company. [Id. at 11:23–25; Nov. 2 Tr. at 90:9–22]. Prior to joining SCRMI, Dr. Kimbrel had worked with MSCs at Dana Farber Cancer Institute ("Dana Farber"). [Nov. 3 Tr. at 7:13–21, 10:1–4, 17:24–18:1].

In 2007, before Dr. Kimbrel joined Dr. Lanza at SCRMI/ACT, Dr. Lanza published a paper in Nature Methods that described a method he and his team had developed to create hemangioblasts ("HBs") from human ESCs ("hESCs"). [Nov. 2 Tr. at 96:21–97:1]. HBs are cells with the potential to become a range of other cells, including vascular and immune cells. [Id. at 95:23–96:1]. Prior to this, no one had been able to create HBs from hESCs. [Id. at 96:2–9]. The method involved two steps: first, hESCs were turned into embryoid bodies ("EBs"), then the EBs were exposed to various cytokines and other conditions that turned them into HBs. [Id. at 97:9–18]. Dr. Lanza was named as an inventor on a patent for the method, along with Dr. Shi-Jiang (John) Lu, who was the Director of Research at ACT during the relevant period. [Nov. 2 Tr. at 97:19–98:1, 98:23–99:4; TX 41 (patent)].[5]

[4] The Court refers to ACT and/or SCRMI based on the timing of specific events (e.g., whether they occurred when ACT or SCRMI were the operating entities, rather than Astellas). The Court will, however, refer to the protocol at issue in this case as the Astellas protocol despite the fact that it was developed at ACT and SCRMI.

[5] Trial exhibits are referred to as [TX __].

In September 2009, Dr. Lanza forwarded to Dr. Lu a 2008 company profile for Pluristem Therapeutics, Inc. that was featured in the publication Regenerative Medicine. [Nov. 2 Tr. at 101:6–102:7; TX 38 (email with attachment)]. The company profile described Pluristem's work with placenta-derived MSCs to treat a variety of autoimmune and degenerative disorders. [TX 38; Nov. 2 Tr. at 102:8–18]. The profile also included a graphic that listed a variety of potential therapeutic uses for the MSCs, including immunological disorders and multiple sclerosis ("MS"). [TX 38; Nov. 2 Tr. at 102:19–103:6; Nov. 3 Tr. at 18:14–23]. Dr. Lanza asked Dr. Lu to look at the profile and proposed that ACT see if it could "isolate ESC-derived cells with similar characteristics/immunomodulatory properties." [TX 38]. Dr. Kimbrel was put in charge of the company's lab work in support of Dr. Lanza's proposal, namely determining whether their HBs could be differentiated into MSCs with immunomodulatory properties. [Nov. 2 Tr. at 103:7–10; TX EZ (Dr. Lu forwarding Dr. Lanza's September 2009 email to Dr. Kimbrel, stating that "[Dr. Lanza] is really interested [in] whether our hemangiobla[s]ts will be able to differentiate into MSCs")].

By the end of 2009, Dr. Kimbrel had found a way to derive MSCs from hESCs using HBs as an intermediary. [Nov. 2 Tr. at 105:1–10; Nov. 3 Tr. at 17:20–23]. The MSCs created through this method are called HB-MSCs. Dr. Kimbrel compared the proteins on the surface of the HB-MSCs that she had created to confirm that they expressed the same surface proteins as MSCs derived through other methods. [Id. at 23:18–24:1, 30:18–24]. She started with the method described in Dr. Lanza's 2007 article, but made several adjustments to create the HB-MSCs. First, she removed erythropoietin ("EPO") from the "recipe" for making HBs, which suppressed the resulting MSCs' tendency to differentiate into vascular cells. [Nov. 3 Tr. at 24:9–24, 25:21–26:1]. Second, she used a substrate called matrigel. [Id. at 29:3–14]. Third, she

increased the amount of beta fibroblast growth factor ("bFGF") used to 30ng/ml. [TX 11]. Lastly, she used alpha minimum essential medium ("aMEM") +20% fetal bovine serum ("FBS"). [Id.].

The benefits of deriving MSCs through an HB-intermediary include that HBs readily expand into large numbers, thereby allowing the creation of more MSCs which is necessary for therapeutic use in humans, and they are also cryo-preservable for later use. [Nov. 3 Tr. at 19:24–20:8]. At the time, MSCs derived from other methods produced limited numbers of MSCs that, when expanded, could lose their potency. [Id. at 20:9–21]. By March 2010, Dr. Kimbrel recorded the ability to generate over four times more MSCs through her method as opposed to an existing direct plating method, though she was sometimes able to generate twenty times more MSCs. [Id. at 34:13–14, 35:22–36:16; TX IA]. Because ACT/SCRMI did not yet have a means of testing the new cells, Dr. Kimbrel froze the HB-MSCs until the company could set up in vivo testing in animal models. [Nov. 3 Tr. at 32:4–16].

C. Drs. Wang and Xu

During the time period in question, Dr. Xu was an Associate Professor at the UConn Health Center ("UConn") and Director of its Stem Cell Institute, [ECF No. 218–1 ¶ 21], and Dr. Wang was a post-doc in Dr. Xu's lab at UConn, [id. ¶ 20]. After attending medical school, Dr. Xu studied immunology and later worked on culturing and studying hESCs. [Nov. 16 Tr. at 7:12–15, 11:18–24]. In 2006, he obtained a patent for a method of generating primate trophoblasts ("TBs") from ESCs. [Id. at 13:22–14:14; TX YE (patent)]. In 2005, Dr. Xu joined UConn, where he trained scientists to culture and differentiate ESCs and also worked on deriving new hESC lines. [Nov. 16 Tr. at 18:18–22, 19:17–23]. Beginning around 2008, Dr. Xu worked with a colleague to differentiate induced pluripotent stem cells ("iPS") into MSCs. [Id. at

23:21–24:4, 24:13–25:2]. Dr. Wang studied immunology and autoimmune diseases, though he did not work with ESCs until he joined Dr. Xu's lab at UConn in 2008. [Nov. 9 Tr. at 15:7–18, 16:18–17:19, 22:11–13]. Prior to hiring Dr. Wang, Dr. Xu had not studied autoimmune diseases. [Nov. 16 Tr. at 139:9–12]. While working with Dr. Xu in 2009 and early 2010, Dr. Wang worked on differentiating ESCs and studying cell adhesion and signaling pathways. [Nov. 9 Tr. at 22:4–8, 23:5–16; Nov. 16 at 26:22–25].

In early 2010, Drs. Wang and Xu began researching and writing a book chapter on stem cells for a textbook on regenerative medicine. [Nov. 9 Tr. at 24:7–25:5; Nov. 16 Tr. at 28:5–16; TX BW]. Dr. Xu asked Dr. Wang to write sections of the book chapter on stem cell differentiation and MSCs. [Nov. 9 Tr. at 24:24–25:18]. As Dr. Wang described it, he researched these areas and presented current thinking in the field, as well as predictions for future directions for research and development. [Id. at 26:11–27:3]. The chapter did not include the results of any new research performed by Drs. Wang and Xu. [Nov. 16 Tr. at 146:2–18]. Dr. Xu reviewed Dr. Wang's writing for accuracy and "to smooth the language," [Nov. 9 Tr. at 27:20–22], and they finished the chapter in May 2010. [Nov. 16 Tr. at 29:14–18].

D. The Collaboration

Astellas regularly engaged in collaborations with academic labs to test its experimental cells in animal models. [Nov. 2 Tr. at 91:12–22]. For Astellas, the goal of these collaborations was to discover whether its cells could work to treat a particular disease in order to help determine whether the cells could be developed into a drug therapy. [Id. at 91:23–92:7; Nov. 3 at 39:15–19]. For example, Astellas has partnered with academic labs at the University of Utah, Harvard University, Stanford University, and others to test its cells in animal models in connection with potential treatments for blindness, kidney disease, and cardiovascular disease.

[Nov. 2 Tr. at 92:16–93:10]. For Astellas' academic partners, the goal of these collaborations is scientific publication, which is "currency" in the academic world as it leads to tenure and can help secure grants. [Id. at 93:11–21; Nov. 3 at 39:5–14; Nov. 4 at 96:12–18]. This type of commercial and academic collaboration is common in the industry and is not unique to Astellas. [Nov. 4 Tr. at 15:16–16:5, 95:19–25].

As noted above, once Dr. Kimbrel had developed a method to create HB-MSCs, she and her team needed to test these new cells in animal models (in vivo) to determine whether they would have a therapeutic effect similar to that of MSCs derived using other methods. [Nov. 2 Tr. at 105:11–18]. They therefore arranged for scientists at the University of Florida to test the cells as a potential treatment for pain. [Nov. 2 Tr. at 106:5–7]. In addition, they arranged for two collaborations with the University of California, Los Angeles ("UCLA") to test the cells as a potential treatment for uveitis and lupus, two autoimmune diseases. [Id. at 106:8–13]. They also established a collaboration with Drs. Wang and Xu at UConn. [Nov. 2 Tr. at 106:14–24].

The UConn collaboration came about through an existing friendship between Drs. Lu and Xu. [Nov. 16 Tr. at 29:22–24]. Dr. Xu recalled introducing Dr. Wang to Dr. Lu at a conference in June 2010, [id. at 30:1–7], though Dr. Wang could not remember when he met Dr. Lu, [Nov. 9 Tr. at 38:2–22]. At the conference, Dr. Lu told Dr. Xu that ACT had developed a new method for deriving MSCs. [Nov. 16 Tr. at 30:11–13]. Drs. Lu and Xu then discussed working together to test the HB-MSCs. [Id. at 30:13–14 ("Now, he said why not see—I said why not to have a collaboration with him.")].

Dr. Xu recalled proposing that Dr. Wang work on testing the HB-MSCs given Dr. Wang's experience working with autoimmune disease models. [Nov. 16 Tr. at 30:15–17, 31:12–17]. Dr. Wang's recollection differed, in that he thought he proposed testing the

HB-MSCs in autoimmune disease models during a meeting with Dr. Lu at ACT in July 2010. [Nov. 9 Tr. at 38:10–24, 39:14–19]. The disease model they discussed with Dr. Lu is called the experimental autoimmune encephalomyelitis ("EAE") model, which mimics the effects of MS in mice, making it a useful model for testing potential MS treatments for humans. [Nov. 4 Tr. at 29:23–30:3, 33:5–19]. Dr. Wang indicated that "the EAE mouse model is easy to start with." [TX 16 (7/26/10 email exchange)].[6]

Prior to the collaboration with ACT, Dr. Xu had not previously collaborated with a commercial company. [Nov. 16 Tr. at 33:25–34:2]. He testified that he did not recall discussing the contours of the collaboration during the early meetings with ACT, but said that he assumed it would function as a "regular academic collaboration." [Id. at 34:3–8]. He said that in his mind, he and Dr. Wang were leading the project because they "only needed [ACT's] cells" and most of the work would be done in his lab. [Id. at 34:20–35:1]. Dr. Wang testified that he understood he and Dr. Xu would be sharing ideas, lab results, and expertise with Astellas. [Nov. 9 Tr. at 43:6–16]. ACT did not pay Drs. Wang and Xu for their work on the collaboration. [Nov. 9 Tr. at 105: 14–17; Nov. 16 Tr. at 91:12–15]; see [Nov. 4 Tr. at 204:4–9 (noting that Drs. Wang and Xu were not paid a salary but were provided certain testing supplies); Nov. 3 Tr. at 39:5–10 (same)]. ACT and Drs. Wang and Xu did, however, agree to co-author an article with ACT that would discuss the results of their collaboration. [TX IB; TX 27; Nov. 3 Tr. at 39:5–10].

[6] Dr. Wang was unable to test the EAE model in mice at UConn in 2010 because Dr. Xu's lab was not approved for animal testing. [Nov. 16 Tr. at 56:20–25]. Instead, Dr. Wang worked with his former colleagues at Yale to set up the testing. [Id. at 56:24–57:4; Nov. 9 Tr. at 158:10–16]. Approximately one year later, by June 2011, Dr. Xu's lab had permission from UConn to use the EAE model in mice. [Nov. 9 Tr. at 159:17–21; Nov. 16 Tr. at 57:19–58:2]. For the experiments done at both Yale and UConn, a kit and standard EAE model protocol were used. [Nov. 9 Tr. at 160:11–12; TX A at 53:11–19 ('551 patent, describing use of kits and standard protocol for the EAE model)]. Some of those kits were purchased by ACT and provided to Drs. Wang and Xu. [Nov. 9 Tr. at 162:16–25].

After meeting with Drs. Wang and Xu at ACT in July 2010, Dr. Lu connected them with Dr. Kimbrel. [Nov. 9 Tr. at 42:6–9; TX 16]. In late July and early August 2010, Drs. Kimbrel and Wang exchanged emails about the collaboration. [TX 17]. Dr. Kimbrel asked Dr. Wang for more information about the EAE model, and he responded by citing literature that showed the model had been used to demonstrate the effectiveness of using MSCs to suppress immune function. [Id.]. In addition, he noted that some studies had shown that MSCs derived from hESCs had stronger immunosuppressive effects than BM-MSCs. [Id.]. He and Dr. Kimbrel arranged to meet at ACT in early August to discuss design of the EAE model experiment and to provide Dr. Wang with some of the HB-MSCs. [Id.]. Prior to the collaboration, Dr. Kimbrel had never run the EAE model. [Nov. 3 Tr. at 42:16–17].

On August 11, 2010, Drs. Wang and Xu visited ACT, and Dr. Kimbrel gave them vials of the frozen HB-MSCs. [Nov. 3 Tr. at 43:25–44:9; TX 11]. During their meeting, it was decided that it would be easier to give Dr. Wang the protocol for making HB-MSCs rather than him having to drive back and forth to ACT to pick up cells for use in the EAE model. [Nov. 3 Tr. at 44:13–18]. That same day, Dr. Kimbrel sent Dr. Wang an email attaching the protocol for making HBs from hESCs, and noting that it was different than the method described in Dr. Lanza's 2007 Nature Methods article. [TX 11; Nov. 9 Tr. at 48:19–49:7]. Dr. Kimbrel's email went on to describe how she had modified the method and how she used it to create HB-MSCs. [TX 11; Nov. 9 Tr. at 173:25–174:22].

Following receipt of this information, Drs. Wang and Xu were to use Dr. Kimbrel's method to make their own cells for use in the EAE model. [Nov. 3 Tr. at 44:14–18]. At one point, Dr. Kimbrel went to Dr. Xu's lab to drop off some cells and Dr. Wang asked her to look at the cells he was trying to create using her protocol. [Id. at 49:6–12]. Dr. Kimbrel looked at the

cells and saw that the HBs were sticking to the bottom of the plate. [Id. at 49:12–19]. She identified the problem as being related to the type of plates he was using to culture the cells and recommended a solution. [Id.].

1. Agreements Regarding Confidentiality

The parties never entered into a confidentiality or non-disclosure agreement governing their collaboration. In January 2012, nearly one and a half years after the parties began collaborating, ACT sent Drs. Wang and Xu a draft material transfer agreement ("MTA"). [TX UB; Nov. 2 Tr. at 163:19–24]. One of the provisions of the draft MTA, set forth in Section 4, limited Drs. Wang and Xu's use of ACT's HB-MSCs to academic research in connection with the EAE model and precluded commercial use. [TX UB]. In addition, Section 4 required that any inventions derived from the materials be disclosed and licensed to ACT. [Id.]. During his testimony, Dr. Lanza described this as a standard MTA that ACT used with its collaborators around this time period. [Nov. 2 Tr. at 163:14–18]. Later that month, a UConn employee contacted Drs. Kimbrel, Lanza, and Lu (copying Drs. Wang and Xu) to propose changes to the draft MTA. [TX XU]. One of the proposed changes would have modified the licensing requirement in Section 4 to allow ACT to use any of Drs. Wang and Xu's inventions internally, but not commercially. [Id.] Several weeks later, an ACT employee responded that ACT would not agree to the proposed changes to Section 4 as they might block ACT's ability to commercialize a product using its own cells. [TX XV]. Ultimately, Drs. Wang and Xu did not enter into an MTA with ACT. [Nov. 2 Tr. at 170:17–20].

There was nevertheless a general understanding among the collaborators that the information being shared was confidential. For one, the protocol for making HBs from hESCs that was attached to Dr. Kimbrel's August 11, 2010 email included the message, "Confidential,

do not distribute!" in bold. [TX 11]. Dr. Kimbrel testified that she expected Drs. Wang and Xu to keep the HB-MSC protocol, which included her additions, confidential because it was new and had not yet been published. [Nov. 3 Tr. at 45:3–14]. Drs. Wang and Xu testified that at the time they understood that the protocol and information provided by ACT were confidential, and Dr. Wang further testified that he had agreed not to share this information with third parties. [Nov. 9 Tr. at 173:2–17, 174:23–175:10; Nov. 16 Tr. at 124:11–15].[7] Subsequent communications between Drs. Kimbrel, Wang, and Xu continued to make clear that the information that had been shared by ACT/Astellas—the cells, Dr. Lanza's original protocol, Dr. Kimbrel's modifications to the protocol, and additional data—were not to be disclosed and were confidential.

For example, in March 2011, Drs. Kimbrel and Wang exchanged emails in response to a request from Dr. Wang for data that he could use in "some school presentations." [TX 39]. Dr. Kimbrel responded,

> As we are a company and have not yet filed our patent for the MSC stuff, please DO NOT distribute the slides to anyone else. The data should only be used for your internal departmental presentation or Xu Lab meetings. Please please do not use the data for any other purposes. This is very important for our viability as a company!

[Id.]. Dr. Wang replied, "I will only use it for departmental presentation." [Id.].

In November 2011, Dr. Kimbrel wrote to Drs. Wang and Xu, notifying them of Dr. Lanza's concerns about protecting ACT's legal rights and stating again that the company was working on a patent application. [TX IB]. Dr. Kimbrel let them know that "ACT is particularly

[7] Dr. Wang testified at trial that he now believes the protocol was not confidential when it was given to him in 2010, despite the confidentiality statement on the document, because he believes the information had been published by August 2010. [Nov. 9 Tr. at 172:10–173:1]. This contradicts testimony from Dr. Kimbrel and her August 11, 2010 email to him in which she noted that the protocol was different than what had been published. [Nov. 3 Tr. at 44:10–25; TX 11].

interested in developing our [HB-MSCs] as a therapeutic product," and suggested a meeting to discuss the continuation of their collaboration. [Id.]. Dr. Xu responded, saying that he was happy about the progress of the collaboration and agreeing to meet to discuss next steps. [Id.].

In early December 2011, following up on her November email, Dr. Kimbrel wrote to Drs. Wang and Xu and told them that "[d]ue to legal implications and intellectual property rights concerning the very use of our [HB-MSCs], we need to clearly define and agree upon" several points. [TX 25]. She stated that ACT wanted to engage in collaborations that would explore novel uses for its products and that one goal of collaboration was publication in a high-impact scientific journal. [Id.]. She reiterated that "[d]etailed, proprietary protocols, cells, and preliminary data offered by ACT must be kept in the strictest of confidence. Collaborators are NOT to share any cells or protocols with third parties without the explicit written consent of ACT." [Id.]. Dr. Xu responded to her email, stating "I don't think I have any problem with these." [Id.]. Dr. Kimbrel understood his response to mean that he was agreeing to the terms of her email. [Nov. 3 Tr. at 57:1–5].

Several months later, on April 2, 2012, as more fully set forth below, Dr. Kimbrel wrote to Drs. Wang and Xu to discuss authorship and planned publication of data from their collaboration. [TX 27]. At the end of her email, she reiterated that "our company's very existence depends upon maintaining control of proprietary methodology that we generate here." [Id.]. Drs. Xu and Wang both responded positively to this email without indicating an issue about the need for confidentiality. [Id.]. The following day, Dr. Kimbrel wrote to Dr. Wang, providing slides with data and noting, "[a]s mentioned before, these cannot be used or shared outside of your lab meeting." [TX GT].

2. Agreements Regarding Authorship

In addition to reaching an understanding about the confidential nature of the information being shared, the parties also discussed authorship arrangements for planned scholarly articles on the results of their collaboration. For example, in November 2011, Dr. Lu proposed an authorship arrangement "for future publications" based on "our previous collaboration experiences with other academic collaborators . . . ." [TX IB]. Dr. Xu responded, saying that he agreed with Dr. Lu's authorship proposal in principle, but that if they disagreed, he and Dr. Wang "could publish [their] own separately according to different focuses. Of course, [ACT] will coauthor [Drs. Wang and Xu's] paper." [Id.]. In December 2011, Dr. Kimbrel proposed the following arrangement: equal co-authorship with collaborators on any publication involving work with ACT cells. [TX 25]. Dr. Xu indicated that he did not have a problem with her proposal. [Id.].

In the April 2012 email referenced above, Dr. Kimbrel wrote to Drs. Wang and Xu with a new proposal for authorship. [TX 27]. She noted that ACT had in vitro data that was not related to the EAE data being generated in Dr. Xu's lab. [Id.]. In order to give the in vitro and EAE model (in vivo) data sufficient attention, she proposed publishing separate papers on each. [Id.]. Dr. Kimbrel told Drs. Wang and Xu that the paper with ACT's in vitro data would "be the first description of [ACT's] patented method." [Id.]. She offered to include Drs. Wang and Xu as authors on this "methods" paper if they would be willing to share a small amount of in vivo data (one figure) for inclusion in the paper, and also offered to let them use some of ACT's in vitro data in the EAE paper. [Id.]. Dr. Xu responded that same day, saying "We like your suggestions. Let's move on [them] asap." [Id.]. Dr. Wang also responded, saying "Yes we agree on your suggestion . . . ." [Id.; TX GT].

E. Drs. Wang and Xu's Alleged Contributions

After Dr. Kimbrel provided Drs. Wang and Xu with her protocol for making HB-MSCs, they made certain modifications to the protocol and suggestions as to how to use HB-MSCs. Dr. Wang focused his efforts on modifying the protocol so that it would be workable for a commercial therapeutic, and said at trial that he felt his additions to the protocol provided "a big step to clinical" trials. [Nov. 9 Tr. at 92:1–4]; see also [id. at 65:18–25 (Dr. Wang's testimony that using a GSK3 inhibitor would improve commercial development of HB-MSCs)].[8] Dr. Xu also testified that he felt he and Dr. Wang made significant contributions to the collaboration with Astellas. [Nov. 16 Tr. at 91:16–19]. Never having worked on a collaboration with a commercial company before, Dr. Xu testified that he would not have agreed to the project if he had been told not to try to improve the protocol given to him by Astellas. [Id. at 38:18–39:2]. He wanted to innovate and felt that was his prerogative during the collaboration. [Id.].

The central issue in this case is whether the modifications that Drs. Wang and Xu made to the protocol were inventive or obvious and already known in the art. These modifications include (1) comparing HB-MSCs to BM-MSCs; (2) using HB-MSCs to treat MS; (3) screening HB-MSCs for low levels of a particular cytokine (IL-6); (4) mitotically inactivating the HB-MSCs; and (5) using a feeder- and serum-free method (a GSK3 inhibitor) to cultivate the HB-MSCs.

1. Comparing HB-MSCs to BM-MSCs

BM-MSCs are considered the benchmark, or gold standard, of MSCs. [Nov. 3 Tr. at 96:24–97:9; Nov. 4 Tr. at 23:15–16, 85:16–18]. Defendants' expert, Dr. Bruce A. Bunnell,

[8] Dr. Wang's interest in working on the commercial side of research was evident in his efforts to seek employment with ACT. [Nov. 9 Tr. at 110:17–111:2].

testified that comparing novel MSC types to BM-MSCs is a necessary step that he and others were performing as early as 2010. [Nov. 10 Tr. at 130:23–131:25; id. at 72:20–73:6 (describing BM-MSCs as a gold standard for comparison to new cell types)]. Dr. Xu also testified that it was "very common," even in 2010, to compare other types of MSCs to BM-MSCs. [Nov. 16 Tr. at 149:8–10, 149:25–150:2, 150:9–12]. In their 2010 book chapter, Drs. Wang and Xu cited to a 2009 article when noting that "[i]t has been shown that human [ESC]-derived MSCs have even stronger immunosuppressive activity than the BM-derived MSCs," indicating prior comparisons of hESC-derived MSCs to BM-MSCs. [TX FD at AIRM00297947].

When conducting experiments on various cytokine levels in HB-MSCs in March 2012, Dr. Kimbrel compared the results to BM-MSCs. [Nov. 3 Tr. at 74:22–75:2; TX 43]. In addition, Dr. Kimbrel testified that "the point of what we were doing is to compare [HB-MSCs] to [] other tissue types as a positive control." [Nov. 3 Tr. at 81:2–19]. Dr. Lanza also testified that BM-MSCs were the standard against which scientists tested other MSCs. [Nov. 2 Tr. at 123:20–124:6]. This comports with testimony from Astellas' expert, Dr. Lisa A. Fortier, that "the first step you would do . . . [is] compare your new MSC against other MSCs, that would be the first and most obvious thing to do." [Nov. 4 Tr. at 83:8–14]. Finally, scientific articles dating back to 2005 indicate that scientists consistently tested and measured new types of MSCs against BM-MSCs. [Id. at 85:7–18; TX HV (2005 article by Dicker et al. comparing properties of adipose-derived MSCs to BM-MSCs); TX GR (2008 article by Trivedi et al. comparing properties of hESC-derived MSCs to BM-MSCs); TX HP (2008 Qiao et al. article comparing properties of umbilical cord blood-derived MSCs to BM-MSCs)].

Given the evidence presented, the Court finds that comparing BM-MSCs, which were the gold standard of MSCs, to new types of MSCs was known in the field and known to Drs. Kimbrel, Lanza, Wang, and Xu prior to the collaboration.

2. Using HB-MSCs to Treat MS

Drs. Wang and Xu claim that they had the idea of using HB-MSCs to treat MS because they offered to test the cells in the EAE model, which was used for testing potential MS treatments. [Nov. 9 Tr. at 39:20–40:4, 41:1–9; Nov. 16 Tr. at 31:12–32:2]. It is clear, however, that Drs. Kimbrel and Lanza—as well as the field in general—were already aware that MSCs could be used to treat MS, an autoimmune disease. For example, in a section of the 2010 book chapter that Drs. Wang and Xu co-authored, they wrote that "[i]t has also been shown that MSCs have [an] immune suppressive function, which is being used to treat autoimmune disease," and cited to a 2007 article titled *Mesenchymal stem cells: A new strategy for immunosuppression?* [TX FD at AIRM00297946].

Before the UConn collaboration began, Dr. Lanza had proposed attempting to make HB-MSCs for the purpose of immunomodulatory therapies. [TX 38]. The article he referenced in the email outlining his proposal specifically mentioned MS as a potential disease target for MSCs. [Id.]. In addition, once the HB-MSCs had been developed, ACT engaged in multiple studies to test the effectiveness of HB-MSCs in treating autoimmune diseases. [Nov. 2 Tr. at 106:8–13 (Dr. Lanza testimony on the UCLA studies on uveitis and lupus)]. As the parties began their collaboration, Dr. Wang wrote to Dr. Kimbrel, sharing citations to multiple articles that he said showed that "[b]oth mouse and human MSC[s] have been used to ameliorate EAE (an autoimmune disease)." [TX 11].

Multiple scientific articles predating the collaboration showed that MSCs could treat autoimmune diseases in general, as well as MS specifically. Dr. Fortier discussed articles from as early as 2005 showing that MSCs, including human MSCs, successfully treated mice induced with disease using the EAE model. [Nov. 4 Tr. at 28:12–24, 34:10–15, 35:10–25, 36:15–16, 36:20–37:20, 38:17–39:6; TX 60 (2005 Zappia et al. article); TX HU (2005 Zhang et al. article); TX 58 (2008 Gordon et al. article)]. Drs. Wang and Xu cited some of these articles in the '551 patent in support of their statement that "MSCs have been found efficacious in the treatment of mice with [EAE], a well-recognized animal model of MS . . . ." [TX A (Col. 2:26–29)].

Scientific articles published prior to the collaboration also showed that MSCs had been used with some success in human clinical trials to treat MS. Defendants cited some of these articles for this same proposition in the '551 patent and their co-authored article with Drs. Kimbrel and Lanza. [TX A (Col. 2:26–33); TX 9]. Dr. Fortier discussed several of these articles, beginning with a 2005 article which referenced disease improvement in clinical trials where MSCs were used to treat MS. [Nov. 4 Tr. at 41:7–44:12; TX HL (2005 Mohyeddin Bonab et al. article); TX HM (2007 Mohyeddin Bonab et al. article)]. It was understood that MSCs derived from hESCs showed as much potential for therapeutic use in patients as MSCs derived from other sources. [Nov. 4 Tr. at 47:4–7, 47:16–48:12, 49:11–17; TX 59 (2006 Olivier et al. article); TX GR (2008 Trivedi et al. article)].

The evidence presented at trial demonstrates that using MSCs to treat autoimmune diseases, including MS, was already being done in the field and was known to Drs. Kimbrel, Lanza, Wang, and Xu prior to the collaboration. In addition, the evidence shows that Dr. Lanza had the idea to use HB-MSCs to treat autoimmune diseases, including MS, prior to the collaboration.

3. IL-6 Levels

Interleukin 6, or IL-6, is one of the cytokines secreted at varying levels by certain types of MSCs. [Nov. 4 Tr. at 20:4–12, 58:13–22; Nov. 3 Tr. 72:9–14]. Because IL-6 has a proinflammatory effect that causes T Cell proliferation, low IL-6 levels are desirable in therapeutics targeting autoimmune disorders. [Nov. 4 Tr. at 70:16–25]. Astellas' expert, Dr. Fortier, walked through scientific articles dating back to 1996 that indicated, first, that MSCs can secrete measurable IL-6 levels, and second, that high IL-6 levels were associated with several autoimmune diseases. [Id. at 71:5–72:22, 73:23–75:2]; see, e.g., [TX HF (1996 Haynesworth et al. article indicating that MSCs secrete IL-6 and that IL-6 levels can be reduced under certain conditions); TX HH (2002 Ishihara et al. article noting that high levels of IL-6 were recorded in connection with several autoimmune diseases)].

Defendants' expert, Dr. Bunnell, testified that, during the time period at issue, BM-MSCs expressed high levels of IL-6 and that scientific thinking at that time was that IL-6 had an anti-inflammatory potential that would be useful in treating diseases like MS. [Nov. 10 Tr. at 76:14–24]; see [Nov. 9 Tr. at 79:20–80:4 (Dr. Wang's testimony)]. As a result, he believed that Drs. Kimbrel and Lanza would have been surprised to learn that a low IL-6 level in HB-MSCs indicated that they could have a better therapeutic effect on autoimmune diseases. See [Nov. 9 Tr. at 80:19–81:15]. This is contradicted by the articles that Dr. Fortier reviewed and discussed at trial, which clearly showed a correlation between high levels of IL-6 and the progression of autoimmune diseases. [Nov. 4 Tr. at 71:5–72:22, 73:23–75:2 (discussing articles)].

Dr. Lanza testified that it was well-known prior to 2010 that IL-6 was pro-inflammatory and that his lab would routinely test the various MSC types they generated to determine what kinds of cytokines they produced, including testing for IL-6. [Nov. 2 Tr. at 122:9–20].

Dr. Kimbrel testified that she was interested in which cytokines were secreted by the HB-MSCs, including IL-6, in order to identify the "unique fingerprint" of the HB-MSCs in contrast to other types of MSCs. [Nov. 3 Tr. at 77:2–13].

In early February 2012, Dr. Kimbrel ordered a custom antibody array to test the levels of twenty specific cytokines secreted by HB-MSCs, including IL-6, as compared to BM-MSCs. [Nov. 3 Tr. at 72:9–73:14; TX HY]. An antibody array can be used to test which proteins are being secreted by cells and at what level. [Nov. 10 Tr. at 78:10–25]. On March 28, 2012, Dr. Kimbrel created a PowerPoint presentation displaying the results of the array testing in which she had compared HB-MSCs to BM-MSCs. [TX 43]. The results showed that HB-MSCs expressed IL-6 at low levels and that BM-MSCs expressed IL-6 at higher levels. [Id.; Nov. 3 Tr. at 74:22–75:2]; see also [TX 62 (April 2012 PowerPoint with IL-6 data)]. In August 2012, Dr. Kimbrel wrote to a fellow scientist at ACT that "differences in the expression of" several factors, including IL-6, would "be the holy grail . . . useful as QC measure, great for intellectual property and patent protection. In essence, such differences may be the key to in vivo potency or efficacy." [TX NI (alteration in original)].

Several months later, in November 2012, Dr. Wang wrote to Dr. Kimbrel, noting that he and Dr. Xu had tested IL-6 levels in HB-MSCs and in BM-MSCs and found that HB-MSCs expressed much lower IL-6 levels. [TX 46]. Dr. Wang testified that the testing he performed was broad and looked at 30,000 genes (which can indicate cytokine levels) rather than just the 20 cytokines selected by Dr. Kimbrel in her custom array. [Nov. 9 Tr. 87: 4–7].[9] Dr. Kimbrel testified that this was the first time Dr. Wang had discussed IL-6 levels with her and that neither

[9] Dr. Fortier observed that testing RNA versus cytokines or proteins yields similar information. [Nov. 4 Tr. at 79:4–9].

he nor Dr. Xu had previously suggested that she look at IL-6 secretion levels. [Nov. 3 Tr. at 77:20–78:7]. Two months later, in response to a January 2013 email from Dr. Xu, Dr. Kimbrel informed him that she had a small amount of data on IL-6 and that she was not following up on the data, nor was anyone else at ACT. [TX RP]. Dr. Kimbrel testified that she had no need to follow up on her existing IL-6 findings from April 2012 because "[w]e basically had what we needed. We knew that . . . low IL-6 was part of the unique fingerprint of the cells, so . . . we got what we needed, basically." [Nov. 3 Tr. at 78:21–25]. Dr. Fortier testified that Dr. Kimbrel's targeted testing of just twenty cytokines suggests that Dr. Kimbrel knew what cell characteristics she was looking for, whereas Dr. Wang's broad testing was more general and unfocused. [Nov. 4 Tr. at 78:3–17].

Based on the evidence presented, it is clear that it was known in the field prior to the collaboration that low levels of IL-6 were beneficial in MSC-based therapies directed at autoimmune diseases. In addition, Dr. Kimbrel independently determined that HB-MSCs had inherently low IL-6 levels prior to Drs. Wang and Xu's IL-6 level testing.

4. Mitotic Inactivation

Because stem cells have the capacity to differentiate, they cannot be injected directly into the body without taking steps to prevent them from differentiating into teratomas, or tumors, that contain undesirable differentiations such as teeth and intestines. [Nov. 4 Tr. at 53:9–22]. The risk of a stem cell-based therapeutic creating unwanted teratomas was known as early as 2005. [Nov. 4 Tr. at 53:23–54:19; TX GZ (2005 Fujikawa et al. article)]. In order to prevent teratomas from forming, stem cells can be prevented from dividing, or undergoing mitosis, through a process called mitotic inactivation. [Nov. 4 Tr. at 54:20–55:5]. Mitotic inactivation can be

accomplished through irradiation or with the use of a chemical called mitomycin C. [Id. at 55:8–12].

Dr. Bunnell testified that mitotic inactivation of MSCs was not done during the time period at issue because it had the potential to stop the secretions that make MSCs therapeutically efficacious. [Nov. 10 Tr. at 63:10–18]. This testimony was directly contradicted by Dr. Fortier, who cited to articles dating back to 2007 indicating that mitotic inactivation did not stop MSCs (including BM-MSCs and hESC-derived MSCs) from secreting their trophic factors and showing positive effects in treating autoimmune disorders. [Nov. 4 Tr. at 63:3–22; TX GY (2007 Bocelli-Tyndall et al. article); TX HT (2011 Tan et al. article)].

The effects of mitotic inactivation on MSCs were not only known in the field, but were also known by Drs. Lanza, Kimbrel, Wang, and Xu prior to their collaboration. Dr. Lanza testified that his lab routinely used mitotic inactivation prior to 2009, and that it was a safety feature necessary to satisfy regulatory agencies which were aware of stem cells' capacity to form teratomas. [Nov. 2 Tr. at 120:17–121:10]. Dr. Kimbrel testified that she had worked with mitotically inactivated MSCs at Dana Farber, prior to joining SCRMI/ACT. [Nov. 3 Tr. at 79:18–23 ("In my own personal experience while I was at Dana Farber, I also knew that [MSCs] still secrete factors even though you have irradiated them."); id. at 80:6–10]. Finally, Drs. Wang and Xu wrote about mitotic inactivation in their 2010 book chapter, noting that "it is possible to mitotically inactivate MSCs differentiated from human ES cells and use them for clinical trials to avoid the possible tumorigenicity by residual undifferentiated human ES cells." [TX FD at AIRM00297947].

Based on the evidence presented, it was known in the field prior to the collaboration that mitotic inactivation of MSCs could stop teratomas from forming without inhibiting the MSCs'

therapeutic secretions. In addition, Drs. Kimbrel, Lanza, Wang, and Xu were aware of this prior to their collaboration.

5. Feeder- and Serum-Free Method (Use of a GSK3 Inhibitor)

Culturing of hESCs can be done with or without feeder cells, which provide nutrients to hESCs and help them to maintain their undifferentiated state. [Nov. 5 Tr. at 31:12–32:2]. Similarly, hESCs can be cultured with or without serum, which also provides nutrients and metabolites to the cells and helps the cells to proliferate and maintain their undifferentiated state. [Nov. 5 Tr. at 30:3–18; 31:8–11]. In 2005, Dr. Lanza co-authored an article describing a method to culture hESCs serum- and feeder-free. [Nov. 5 Tr. at 33:23–34:13; TX GP]. In addition, Drs. Lanza and Lu's patented method for generating HBs from hESCs involved serum- and feeder-free conditions. [Nov. 5 Tr. at 35:5–17; TX 41]. Dr. Xu testified that serum- and feeder-free conditions for culturing cells were well-known prior to 2010. [Nov. 16 Tr. at 172:19–21, 173:10–12]. There is a preference for serum- and feeder-free culturing at the clinical trial stage of drug development, because serums and feeders are often derived from animals, including mice and cows. [Nov. 5 Tr. at 35:23–36:9]. Eliminating these animal sources of cells helps to reduce the risk of viruses and bacteria being transmitted to humans. [Id.].[10] Prior to clinical testing, however, using serum and feeder is less expensive when first testing a hypothesis. [Id. at 36:17–37:8].

Relevant to this case is the use of a glycogen synthase kinase-3 ("GSK3") inhibitor, such as 6 bromoindirubin-3'-oxime ("BIO") as an alternative to using serum and feeder. [Nov. 5 Tr. at 29:12–15, 38:10–19]. Astellas' expert, Dr. Ali Brivanlou, first discovered BIO and in 2004, wrote about its ability to maintain hESCs in an undifferentiated state without serum or feeder.

[10] Using human feeder cells is an alternative to using animal feeder cells. [Nov. 5 Tr. at 38:3–8].

[Id. at 38:10–15; TX 7 (2004 Sato et al. article)]. His article also indicated that hESCs treated with BIO created more EBs than hESCs. [TX 7 (Figure 5a, showing increased EB formation with BIO); Nov. 5 Tr. at 49:23–50:20].

In his 2004 article, Dr. Brivanlou described using a concentration of 2µm (micromolar) of BIO with hESCs. [TX 7]. In 2006, Dr. Brivanlou contributed to a book chapter in which he further discussed the use of BIO in hESC cultures at various concentrations. [TX 34; Nov. 5 Tr. at 54:25–55:13]. In that discussion, he noted that

> [t]he optimal concentration of the GSK3 inhibitor (BIO) should be predetermined for each hESCs line by testing different combinations of BIO, generally ranging from 1 to 5 µm. . . . It is therefore critical to find out a minimal concentration of BIO that can maintain each hESCs line in the undifferentiated state to avoid any significant effect on their viability or growth rate.

[TX 34]. As Dr. Brivanlou explained at trial, hESCs from different cell lines can have genetic differences, making it necessary to find a concentration of BIO that is appropriate for a specific cell line. [Nov. 5 Tr. 56:2–8]. In addition to the article and book chapter, Dr. Brivanlou also obtained a patent related to BIO which was published in 2009. [TX 33]. The patent describes a broad range of possible concentrations of BIO, from 0.001 µm to 100 µm, that could be used with the method, but also suggests a narrower concentration for the particular cell line described in the patent as "preferably about .01 to about 10µm, and most preferably 1µm." [Id. at 5:[0040]; Nov. 5 Tr. at 58:21–59:4].

In October 2010, Dr. Wang experimented by using BIO with hESCs at step one of the HB-MSC protocol. [TX BT; Nov. 9 Tr at 58:1–11, 212:2–14]. Following Dr. Brivanlou's 2004 article, Dr. Wang first experimented with using BIO at a concentration of 2µm. [TX BT at IMSTEM-0042984; Nov. 9 Tr. at 212:8–213:7]. Approximately ten days after his first experiment, which he described as resulting in cell die-off, he recorded an experiment in his lab notebook in which he used a concentration of 0.25µm of BIO. [TX BT at IMSTEM-0042987;

Nov. 9 Tr. at 214:3–11].[11] A February 2011 PowerPoint presentation drafted by Dr. Wang and sent to Dr. Xu further demonstrated that they were aware of Dr. Brivanlou's work. [TX W]. One slide in the presentation discusses using BIO at 2µm and cites to Dr. Brivanlou's 2004 article. [Id.]. Other slides state that BIO increases EB formation and decreases cell detachment. [Id.]. In reviewing this presentation, Dr. Brivanlou observed at trial that Dr. Wang was describing "exactly what [Dr. Brivanlou] described" in his published work. [Nov. 5 Tr. at 60:11–61:12].

Dr. Wang consistently testified at trial that his addition of a GSK3 inhibitor at step one of the protocol for making HB-MSCs was focused on improving the yield at the middle stage of the protocol (generating EBs). [Nov. 9 Tr. at 56:17–22, 64:9–11, 64:19–65:3, 66:11–17, 198:2–8]. According to Dr. Wang's testimony, however, adding a GSK3 inhibitor, "doesn't change the functionality of the final product MSCs. . . . MSCs derived from GSK or not from GSK, they show the same efficacy in EAEs. . . . the final product, they work the same." [Id. at 198:2–10].[12]

[11] Dr. Wang testified that he might have tested BIO at different concentrations between the dates of these two lab notebook entries, but these are the only lab notebook entries indicating that he experimented with BIO concentrations and he was not able to identify other dates or concentrations that he might have tried. [Nov. 9 Tr. at 214:12–17; id. at 215:1–2 ("Maybe I did more than that, I just did it and I didn't write down."); TX BT].

[12] Given Dr. Wang's repeated statements at trial about why he used a GSK3 inhibitor, the Court does not credit the conflicting testimony offered by Defendants' expert, Dr. John M. Perry, who focused on the "downstream effects" on MSCs when adding a GSK3 inhibitor early in the protocol rather than the intermediate effects (increased EB production prior to MSC formation) described by Dr. Wang. [Nov. 12 Tr. at 34:18–24 (stating that adding a GSK3 inhibitor "has a fundamental downstream effect" on MSCs, so that "if you don't add it, you do not get that product. So it is critical."); id. at 42:15–25 (noting his belief that it was a new idea to use a GSK3 inhibitor for its downstream effects)]. Dr. Perry's testimony was also contradicted by Dr. Brivanlou, who testified that adding a GSK3 inhibitor like BIO is unlikely to have downstream effects on cells. [Nov. 5 Tr. at 108:6–15].

Dr. Kimbrel testified that others in her lab at ACT were culturing cells in feeder-free conditions and that whether or not to use feeders was "a business decision," which was consistent with Dr. Brivanlou's testimony about the cost of not using feeder. [Nov. 3 Tr. at 88:4–14, 129:3–11; Nov. 5 Tr. at 37:3–8]. She also testified that she understood that GSK3 inhibitors could be used to maintain hESCs in an undifferentiated state. [Nov. 3 Tr. at 50:9–25]. Dr. Lanza too testified that he was aware of GSK3 inhibitors and knew that they could be used to culture and maintain hESCs. [Nov. 2 Tr. at 128:5–9].

In light of the evidence presented, the benefits of using a GSK3 inhibitor such as BIO to maintain hESCs in an undifferentiated state were known in the field generally and, more specifically, were known by Drs. Lanza, Kimbrel, Wang, and Xu prior to their collaboration. Further, the benefits of using a GSK3 inhibitor such as BIO to increase EB formation were also known in the field at the time of the collaboration.

F. Drs. Wang and Xu Form ImStem

In September 2011, during the ongoing collaboration with ACT, Drs. Wang and Xu prepared a draft business plan for using hESC-derived MSCs to treat autoimmune diseases. [TX AK]. In that business plan, they included graphics depicting Astellas' process of making HB-MSCs. [Id.; Nov. 4 Tr. at 111:21–112:5]. By June 2012, Drs. Wang and Xu had founded their company, ImStem. [ECF No. 218-1 ¶¶ 20–21, 39]. Dr. Wang admitted that he did not tell ACT that he and Dr. Xu were establishing a competing company. [Nov. 9 Tr. at 252:2–6]. Dr. Wang currently works at ImStem as its Chief Technical Officer, Director, and Vice President. [ECF No. 218-1 ¶¶ 18, 20]. Dr. Xu was the Chief Scientific Officer of ImStem and is now on its Scientific Advisory Board. [Id. ¶ 21]. Both Drs. Wang and Xu currently own shares of ImStem. [Id. ¶¶ 22–23].

Dr. Xu, after discovering how to derive TBs from hESCs in 2002, continued to research TBs but his focus was on the molecular mechanism for differentiating ESCs into TBs, not on whether they could be used to derive MSCs. [Nov. 16 Tr. at 27:9–15]. At his deposition, Dr. Xu testified that the HB-MSC technology gave ImStem a "shortcut" in the development of TB-derived MSCs ("T-MSCs"). [TX 88 (Xu Depo. Tr. at 75:11–17 ("As I said, we met Dr. Lu and we think, you know, their company is making—generating MSC from ES cells, and so I think that will give us a shortcut to do the test."), id. at 80:02–13 (similar), id. at 84:22–85:4 (similar)); Nov. 16 Tr. at 50:4–16 (explaining that he revised the Astellas protocol to derive MSCs from TBs instead of HBs); TX AI (ImStem progress report in connection with a grant obtained from the State of Connecticut, stating that his and Dr. Wang's research on HB-MSCs as described in the 2014 Stem Cell Reports article contributed to the development of T-MSCs)].[13] Aside from these general representations, however, no evidence was presented regarding how much time, if any, this "shortcut" saved Defendants or what aspect of the Astellas protocol helped them to begin developing T-MSCs. See [Nov. 4 Tr. at 173:23–174:20 (Dr. Fortier testimony that she did not know what Dr. Xu meant by "shortcut" or what aspects of the protocol were used)].

In March 2012, Dr. Xu sent a draft of the ImStem business plan to Dr. Michael Men, one of ImStem's early investors, in which he noted that Dr. Wang had drafted the plan. [TX 19; Nov. 9 Tr. at 186:15–17 (stating that Dr. Men is ImStem's CEO and a "major investor")]. Dr. Wang testified that the goal of the company was to develop proprietary technologies to produce MSCs and use them to treat autoimmune and degenerative diseases. [Nov. 9 Tr. at

[13] Given Dr. Xu's testimony at trial, [Nov. 16 Tr. at 50:4–16], the Court does not find credible his contradictory testimony that the only shortcut he obtained from the ACT collaboration was that his lab had already been approved for animal research in connection with the EAE model so that he was then able to test TB-derived MSCs in vivo without having to initiate the approval process. [Nov. 16 Tr. at 59:5–14].

123:25–124:4]. The March 2012 draft business plan included data from the ACT collaboration on HB-MSCs and described ACT's method of deriving MSCs as a method "we have developed" and as "our method." [TX 19 at IMSTEM-0040440]. The draft plan does not disclose that the method was, in fact, ACT's. See [id.]. The March 2012 draft does not mention TBs or T-MSCs, as Dr. Wang acknowledged at trial, see [TX 19; Nov. 9 Tr. at 244:16–21], though he testified that he used the HB-MSC information as a placeholder until he later updated the draft with T-MSC references. [Nov. 9 Tr. at 122:19–23; 125:17–126:1; 126:13–25]. Dr. Wang testified that it was his intention for ImStem to pursue commercializing T-MSCs, [Nov. 9 Tr. at 124:5–14], and he and Dr. Xu have both represented during this litigation that they are currently working to commercialize their T-MSC technology, not HB-MSC technology. [ECF No. 218-1 ¶ 42].

In an April 2, 2012 email exchange, Drs. Wang and Xu communicated with each other regarding patents held by ImStem competitors, including ACT, which they identified as one of ImStem's "major competitors." [TX 26]. This email was sent on the same day that Dr. Kimbrel wrote to Drs. Wang and Xu about their collaboration and told them that ACT's "very existence depends upon maintaining control of proprietary methodology that we generate here." [TX 27]. Defendants' view of ACT as a competitor was reiterated in a series of July 2012 emails exchanged between Drs. Men, Xu, and Wang. On July 3, 2012, Dr. Wang sent a draft patent application stating, "[t]his patent is to prevent ACT[] from using their technology to go to clinic and develop [their] product." [TX Z]. The draft application included a description of and data on ACT's HB-MSC method. [Id.]. Shortly after sending this email, Dr. Wang sent a revised draft patent application, this time telling Drs. Men and Xu that he was including "[m]ore claims . . . for our attack patent." [TX AA]. At trial, Dr. Wang testified that he intended the patent

application, ultimately issued as the '551 patent, to be "a bargaining chip . . . for any future litigation . . . . If anybody sue[d] me, then we can use that as a counterattack . . . to exchange for some kind of licensing exchange and the patent exchange." [Nov. 9 Tr. at 138:1–20].

On July 12, 2012, Drs. Wang and Xu submitted the patent application that issued as the '551 patent. [TX 3]. This application included ACT's protocol for making HB-MSCs. [Id.; Nov. 9 Tr. at 177:6–178:22]. Despite this, as Dr. Wang acknowledged, he did not include Drs. Kimbrel and Lanza as inventors on the patent application. [Nov. 9 Tr. at 140:10–141:6]. Defendants also did not tell ACT that they were applying for a patent related to ACT's HB-MSCs. [Id. at 262:15–22; Nov. 3 Tr. at 65:22–24]. Dr. Wang conceded that he included Astellas' protocol in his patent application and that he disclosed the patent application to UConn before ACT/Astellas had made its protocol public. [Nov. 9 Tr. at 141:7–10, 179:15–19; ECF No. 163 at 8]. Dr. Wang testified that he filed the '551 patent application because he wanted a return on his and Dr. Xu's contributions to the ACT collaboration that he did not think they were getting. [Nov. 9 Tr. at 189:21–190:3].

On June 6, 2012, Drs. Wang and Xu submitted an invention disclosure form to UConn. [TX CN]. In the form, they disclosed having invented a method for deriving MSCs from TBs to create T-MSCs using an intermediary process which was similar to the one developed by Dr. Kimbrel at ACT using HBs. [Id. ("This method we describe here is completely novel for derivation of MSCs from hESCs. Briefly we first differentiate hESCs into trophoblasts . . . . The trophoblasts are then isolated and re-plated onto Matrigel-coated plates. . . .")]. In a section requesting information on third party materials used to generate the invention, Drs. Wang and Xu did not list the protocol or cells provided by ACT. [Id.]. In a section asking for documentation

of the invention, Drs. Wang and Xu listed March 1, 2012 as the date they first conceived of the invention. [Id.].[14]

In addition to sharing and presenting the confidential Astellas protocol to the U.S. Patent and Trademark Office ("PTO"), UConn, and an ImStem investor, in January 2013, Drs. Wang and Xu submitted a grant proposal to the State of Connecticut on behalf of ImStem that described the HB-MSC method as their own. [TX AV at IMSTEM-0018376 ("We have used a novel method to differentiate hESC into MSC via an intermediate hemangioblast (HB) step . . . .")]. Dr. Xu testified that he applied for the grant using ImStem's name because he believed it would increase their chances of getting the grant and using the funds to promote commercial and therapeutic applications of stem cells. [Nov. 16 Tr. at 89:15–25; TX AV]. Dr. Wang admitted that he did not tell ACT about the grant application. [Nov. 9 Tr. at 224:10–12]. Dr. Wang also testified that he included figures obtained from Dr. Kimbrel in the ImStem grant application. [Nov. 9 Tr. at 241:24–242:4, 244:6–12].

Defendants later misrepresented HB-MSC results as T-MSC results to promote the benefits of their T-MSC technology. At trial, Dr. Wang admitted that at least three documents he submitted to various entities contained graphs displaying HB-MSC results that he had labeled as displaying T-MSC results. [Nov. 9 Tr. at 267:17–268:4, 269:14–22, 271:10–273:8]. These graphs were included in a 2014 article that he and Dr. Xu co-authored with Drs. Kimbrel and Lanza to describe the results of their collaboration. [Nov. 9 Tr. at 267:17–269:2; TX 9]. Dr. Wang included the mislabeled graphs in a poster presentation he created, a 2013 grant application submitted to the State of Connecticut (which was signed under penalty of perjury),

[14] At trial, they both stated that they did not provide an accurate date on the form but rather had conceived of the idea prior to March 1, 2012. [Nov. 9 Tr. at 192:18–23; Nov. 16 Tr. at 206:4–17].

and a 2014 filing submitted to the Food and Drug Administration ("FDA") in connection with ImStem's pre-pre-Investigational New Drug application briefings. [TX UH (poster presentation); TX UO (grant application); TX UI (FDA briefing)].[15]

In late June 2013, Dr. Kimbrel found and sent a link to an article that mentioned Drs. Wang and Xu to her colleagues at ACT. [TX NW]. The article stated that Drs. Wang and Xu had formed a new company, ImStem, to "explor[e] the potential for cells derived from human embryonic stem cells to be developed into treatments for multiple sclerosis." [TX WS]. The article also noted that they had a patent pending, [id.], and the subject line to Dr. Kimbrel's email sending the link was "keep eye on UConn patent pending." [TX NW].

Dr. Wang testified at trial that he and Dr. Xu formed ImStem and filed the application for what would become the '551 patent because he felt that he and Dr. Xu were not getting "a proper return" for what they were contributing to the collaboration with Astellas. [Nov. 9 Tr. at 189:21–190:3]. In addition, he testified that he felt the contributions that he and Dr. Xu were making to the protocol and the hard work they put into testing the protocol gave them a right to claim and protect those contributions in a patent. [Id. at 135:17–23; 190:10–14]. Dr. Xu also said that, at least early in the collaboration, he believed he would be able to patent any improvements he made. [Nov. 16 Tr. at 41:14–18]. Dr. Xu estimated that during the four years of the collaboration with Astellas, he spent one third of his time working on the project, [id. at

[15] At trial, Dr. Xu—who testified after Dr. Wang—stated that Figure 4A in the 2014 Stem Cell Reports article showed T-MSC data instead of HB-MSC data and was included in the article by mistake. [Nov. 16 Tr. at 46:1–7; TX 9]. He also stated that Figure 8 in the FDA submission showed T-MSC data, [Nov. 16 Tr. at 45:17–25, 225:9–11], but that Figure 9 did, in fact, show HB-MSC data, [id. at 46:18–22; TX UI]. The Court notes that the graphs shown in the Figures in the article and the FDA filing appear to present nearly identical data, with Figure 8A in the FDA filing adding one additional data point not shown in Figure 4A in the article. [TX 9; TX UI].

90:24–91:4], and Dr. Wang estimated that he spent eighty percent of his time working on the project during that time frame, [Nov. 9 Tr. at 108:18–25].

At trial, Drs. Wang and Xu also suggested that they did not trust Astellas after some of their slides were shown (with attribution to Drs. Wang and Xu) at a 2012 presentation Astellas gave to investors, and that this distrust led to forming ImStem and deciding to file their own patent. See [Nov. 9 Tr. at 256:2–15; TX FI; TX MV]. The timing, however, indicates that Drs. Wang and Xu were already speaking with Dr. Men about forming ImStem and filing for a patent prior to the accidental disclosure. See [TX 19 (March 2012 ImStem business plan); TX MV (email chain discussing disclosure at May 2012 conference)]. Dr. Xu's misunderstanding of the nature of the collaboration is highlighted by his testimony about that 2012 presentation. He testified to being upset that Astellas shared information about the progress of the collaboration with investors, and frustrated that the purpose of the presentation "was to promote their company . . . for their own benefit." [Nov. 16 Tr. at 70:19–71:3]. While Astellas had agreed not to share the data and later acknowledged their mistake in sharing it at the presentation against Drs. Wang and Xu's wishes, [TX MV], the shared data pertained to the tests that Drs. Wang and Xu were performing at Astellas' direction, with Astellas' cells, in order to further Astellas' commercial goals for the cells.

G. End of the Collaboration

As noted earlier, in April 2012, Drs. Kimbrel, Wang, and Xu had agreed that they would publish two separate papers. [TX 27; TX GT]. Drs. Wang and Xu, who would provide one figure with data from the EAE model for use in the article, would be listed as co-authors on a "methods" paper, and they could also publish a separate paper focused on the EAE model results that could include in vitro data from ACT. [TX 27; TX GT; Nov. 2 Tr. at 184:9–17]. It was

contemplated that the methods paper would be published first and, in fact, Dr. Kimbrel specifically told Drs. Wang and Xu that the paper with ACT's in vitro data would "be the *first description* of our patented method," thereby clearly indicating that it would be published before the separate EAE paper. [TX 27 (emphasis added)]. As ACT prepared a draft of its methods paper, however, Drs. Wang and Xu changed their minds and refused to allow ACT to include their in vivo data in that first paper. [Nov. 2 Tr. at 185:2–7]. As a result, instead of using the EAE model data, ACT used data from its two UCLA collaborations. [TX 10; Nov. 16 Tr. at 215:12–16]. That paper was published on March 20, 2014. [TX 10].

The parties initially submitted a manuscript for the EAE model paper in Cell Stem Cell, but the journal rejected the manuscript because, among other enumerated reasons, ACT's March 2014 article contained similar conclusions regarding the effectiveness of the HB-MSCs in treating autoimmune diseases. [TX DZ]. On news of the rejection, Dr. Xu emailed Drs. Kimbrel, Lanza, and Lu, saying "somebody among us killed our own paper." [Id.]. Drs. Wang and Xu testified that they were upset at being "scooped" by the March 2014 ACT article. [Nov. 9 Tr. at 131:5–9; Nov. 16 Tr. at 83:16–84:6]. As noted above, however, they were offered and initially accepted the opportunity to be co-authors on the "first description" of the method in the March 2014 article in exchange for allowing a limited amount of their data to be used in the article, but later changed their minds and rejected the offer. Ultimately, on July 8, 2014, the parties' joint paper on the results of the EAE model was published in Stem Cell Reports. [TX 9]. Although Drs. Wang and Xu described Stem Cell Reports as a "prestigious" journal in a grant progress report submitted to the State of Connecticut, [TX AI], they both testified that it was not as good as Cell Stem Cell and that they were disappointed not to have

been published in what they felt was a superior journal, [Nov. 9 Tr. at 259:10–17; Nov. 16 Tr. at 85:6–13].

The parties' collaboration ended with the publication of their joint paper in Stem Cell Reports. [Nov. 3 Tr. at 65:8–14; Nov. 16 Tr. at 90:19–23; TX 9].

H. Patents Issued

Astellas obtained two patents regarding the technology at issue in this litigation: the '321 patent, which describes the method for making HB-MSCs, and the '956 patent, which describes how the HB-MSCs can be used therapeutically. [TX 1 ('321 patent); TX 2 ('956 patent)]. Astellas is the current owner and assignee of the '321 patent, which issued on February 24, 2015 and is titled "Mesenchymal Stromal Cells And Uses Related Thereto." [ECF No. 218-1 ¶¶ 3–4]. The patent currently lists Dr. Kimbrel, Dr. Lanza, Jianlin Chu, and Nicholas Arthur Kouris as inventors. [Id. ¶ 4]. The application for the '321 patent was filed on November 30, 2012, published on July 18, 2013, and claimed priority to a provisional application that was filed on November 30, 2011. [Id. ¶¶ 5–7]. Astellas is also the current owner and assignee of the '956 patent, which issued on February 24, 2015 and is also titled "Mesenchymal Stromal Cells And Uses Related Thereto." [Id. ¶¶ 8–9]. The patent lists the same four inventors as the '321 patent. [Id. ¶ 9]. The application for the '956 patent was filed on May 30, 2013, published on March 13, 2014, and claimed priority to a provisional application that was filed on November 30, 2011. [Id. ¶¶ 10–12].[16]

ImStem is the assignee of the '551 patent, which issued on August 29, 2017 and is titled "Mesenchymal-like Stem Cells Derived From Human Embryonic Stem Cells, Methods And

[16] Defendants demonstrated at trial that some contents of the '321 and '956 patent were copied and pasted from a grant application Defendants submitted to obtain funding for their

Uses Thereof." [ECF No. 218-1 ¶¶ 24–26]. The patent currently lists Drs. Wang and Xu as inventors, [id. ¶ 27], though at summary judgment the Court ordered that Drs. Kimbrel and Lanza be added to the patent because it includes the steps recited in the Astellas protocol, [ECF No. 163]. The '551 patent claims priority to two provisional applications which were filed on July 12, 2012 and February 11, 2013, and the application that issued as the '551 patent was published on July 23, 2015. [ECF No. 218-1 ¶¶ 29–30].

During patent prosecution, in June 2016, Drs. Wang and Xu provided a patent examiner with citations to Astellas' '321 and '956 patents. [Nov. 12 Tr. at 150:9–12, 151:1–18; TX 40 at AIRM00293876]. The examiner initially rejected the claims in the application, citing issues with anticipation and obviousness related to Astellas' '321 patent. [Nov. 12 Tr. at 149:22–25, 152:1–12; TX 40 at AIRM00295651]. As a result, Drs. Wang and Xu amended Claim 1 to require, rather than recite as optional, the inclusion of a GSK3 inhibitor. [Nov. 12 Tr. at 152:14–153:1; TX 40 at AIRM00295775]. In support of the amendments, Drs. Wang and Xu submitted a copy of a departmental presentation that disclosed that the use of a GSK3 inhibitor, such as BIO, could increase EB production which they said predated Astellas' patents' priority date. [TX 40 at AIRM0295788–93]. The presentation was similar to a draft presentation from February 2011, [TX W], but unlike that draft, the version submitted to the patent examiner did not cite to any of Dr. Brivanlou's publications. [TX 40 at AIRM0295788–93].

After Drs. Wang and Xu's amendment, the examiner allowed the claims, citing the requirement of "adding a GSK3 inhibitor at a specific concentration" as the reason for the

collaboration with Astellas. [TX CC-A; TX 02-A; TX 35-A]. The copied sections, however, included information that Dr. Kimbrel had provided in support of the grant application, [TX FF; TX GW; TX 22], as well as general information about MS and results of the EAE model—which were generated in collaboration with Astellas to test Astellas' HB-MSC cells.

allowance. [Nov. 12 Tr. at 154:2–24; TX 40 at AIRM00295969]. Although the patent indicates that Drs. Wang and Xu disclosed the 2004 Brivanlou article discussing GSK3 inhibitors, [TX A], results from a search of prior art performed by the patent examiner show that he did not identify any materials by Dr. Brivanlou or search for the term "GSK3" or "BIO." [Nov. 12 Tr. at 181:20–182:1, 184:13–185:21, 187:11–188:11, 189:5–24; id. at 191:4–6 ("Q. Nothing in the record would suggest the examiner had Dr. Brivanlou's 2006 or 2009 publication, right? A. That's correct."); TX 40 at AIRM0295975–78].

I. Current Status of Inventions

Neither party had a product on the market based on the HB-MSC technology at issue in this case at the time that Astellas' application for the '321 patent was published on July 18, 2013 (making the Astellas protocol public). [ECF No. 218-1 ¶¶ 5–7]. Nor does either party have a product currently on the market using the HB-MSC technology. [Nov. 2 Tr. at 81:16–18; Nov. 6 Tr. at 48:16–22; Nov. 9 Tr. at 152:1–3; Nov. 13 Tr. at 23:14–24; id. at 26:15–23]. Defendants have a product in clinical trials that is based on their T-MSC technology. [Nov. 16 Tr. at 48:4–6, 48:14–17].

IV. CONCLUSIONS OF LAW

The Court first addresses the parties' inventorship claims and counterclaims and then addresses Astellas' Chapter 93A claim. For the reasons set forth below, the Court finds that Drs. Kimbrel and Lanza are the sole inventors of the methods and uses described in the '321, '956, and '551 patents. In addition, the Court concludes that Astellas has failed to demonstrate that Defendants violated Chapter 93A.

A. Count I; Counterclaim Counts I and II: Correction of Inventorship

At summary judgment, the Court found that Drs. Kimbrel and Lanza were co-inventors of the '551 patent. [ECF No. 163]. The parties continue to dispute whether Drs. Wang and Xu

should be removed from the '551 patent, whether Drs. Wang and Xu should be added to the '321 patent, and whether Dr. Wang should be added to the '956 patent.[17, 18]

"A person who alleges that [he or she] is a co-inventor of the invention claimed in an issued patent who was not listed as an inventor on the patent may bring a cause of action to correct inventorship in a district court under 35 U.S.C. § 256." Vapor Point LLC v. Moorhead, 832 F.3d 1343, 1348 (Fed. Cir. 2016) (quoting Eli Lilly & Co. v. Aradigm Corp., 376 F.3d 1352, 1357 n.1 (Fed. Cir. 2004)), cert. denied sub nom. Nanovapor Fuels Grp., Inc. v. Vapor Point, LLC, 137 S. Ct. 1121 (2017); see 35 U.S.C. § 256 (permitting correction of inventorship "[w]henever . . . through error an inventor is not named in an issued patent"). "Inventorship is a mixed question of law and fact: The overall inventorship determination is a question of law, but it is premised on underlying questions of fact." Eli Lilly, 376 F.3d at 1362.

"Patent issuance creates a presumption that the named inventors are the true and only inventors," therefore, to establish co-inventorship, the alleged co-inventor "must prove [his or her] contribution to the conception of the claims by clear and convincing evidence." Ethicon, Inc. v. U.S. Surgical Corp., 135 F.3d 1456, 1460–61 (Fed. Cir. 1998). "Because '[c]onception is the touchstone of inventorship,' each joint inventor must generally contribute to the conception of the invention." Id. at 1460 (alteration in original) (quoting Burroughs Wellcome Co. v. Barr Lab., Inc., 40 F.3d 1223, 1227–28 (Fed. Cir. 1994)). The Federal Circuit has explained that "[a]ll that is required of a joint inventor is that he or she (1) contribute in some significant

[17] In September 2019, the parties stipulated that inventorship on a patent not in dispute in this litigation, the '122 patent, will be aligned to match the Court's determination on inventorship for the '551 patent. [ECF No. 95; ECF No. 218 at 3 n.2; ECF No. 220 at 16; ECF No. 218-1 ¶¶ 37–38].

[18] The Court previously denied as untimely Dr. Xu's motion to amend his counterclaims to add a claim for correction of inventorship as to the '956 patent. [ECF No. 85].

manner to the conception or reduction to practice of the invention, (2) make a contribution to the claimed invention that is not insignificant in quality, when that contribution is measured against the dimension of the full invention, and (3) do more than merely explain to the real inventors well-known concepts and/or the current state of the art." Israel Bio-Eng'g Project v. Amgen, Inc., 475 F.3d 1256, 1263–64 (Fed. Cir. 2007) (quoting Pannu v. Iolab Corp., 155 F.3d 1344, 1351 (Fed. Cir. 1998)).

"People may be joint inventors even though they do not physically work on the invention together or at the same time, and even though each does not make the same type or amount of contribution." Burroughs Wellcome, 40 F.3d at 1227. A co-inventor does not need to make a contribution to every claim of a patent, Ethicon, 135 F.3d at 1460, nor does a co-inventor need to contribute to the conception of all the limitations in a single claim, Eli Lilly, 376 F.3d at 1361. "On the other hand, one does not qualify as a joint inventor by merely assisting the actual inventor after conception of the claimed invention." Ethicon, 135 F.3d at 1460. In addition, "[a] contribution of information in the prior art cannot give rise to joint inventorship because it is not a contribution to conception." Eli Lilly, 376 F.3d at 1362; see Dana-Farber Cancer Inst., Inc. v. Ono Pharm. Co., 964 F.3d 1365, 1372 (Fed. Cir. 2020) ("It is certainly true that simply informing another about the state of the prior art does not make one a joint inventor."). "The determination of whether a person is a joint inventor is fact specific, and no bright-line standard will suffice in every case." Fina Oil & Chem. Co. v. Ewen, 123 F.3d 1466, 1473 (Fed. Cir. 1997).

1. The '956 Patent

As a starting point, the Court notes that Astellas' collaborators from UCLA and the University of Florida are not listed as inventors on the '956 or '321 patents, though their data is

included in the '956 patent's specification and, in the case of both of the UCLA collaborations, their data was included in a co-authored paper. [Nov. 2 Tr. at 110:7–14; Nov. 3 Tr. at 70:3–71:2; TX 1; TX 2]. This is consistent with multiple examples provided by witnesses, including Drs. Lanza, Xu, and Wang, where an academic collaboration and publication did not result in authors being included as inventors on related patents. [Nov. 2 Tr. at 98:16–99:11 (Dr. Lanza testimony regarding a collaboration with scientists at the University of Florida and Memorial Sloan Kettering Institute); Nov. 9 Tr. at 153:4–154:3 (Dr. Wang testimony regarding differing authorship on a journal article and inventorship on one of his and Dr. Xu's related patents); Nov. 16 Tr. at 155:11–12, 155:19–156:7, 156:25–157:9 (Dr. Xu testimony regarding a co-author on one of his journal articles who was not included as an inventor on a related patent)].

Dr. Wang alleges that he made several significant contributions to the '956 patent and that he should be added as a joint inventor. [ECF No. 221 ¶¶ 120–35]. The alleged contributions include the ideas of using HB-MSCs to treat MS (Claims 3 and 4), of comparing HB-MSCs to BM-MSCs (Claims 10, 11), of screening HB-MSCs for low IL-6 (Claim 9(f)), and of mitotically inactivating the HB-MSCs (Claim 5(a)). [Id.]; see [TX 2 ('956 patent)].[19]

As discussed supra, Section III.E.1–4, the Court has found that these alleged contributions were known in the field and by Drs. Kimbrel and Lanza prior to their collaboration with Drs. Wang and Xu. Because joint inventors must "do more than merely explain to the real inventors well-known concepts and/or the current state of the art," Israel Bio-Eng'g Project, 475

[19] The Court notes that while Defendants frame one contribution as "screening for IL-6," [Nov. 9 Tr. at 142:21–24; Nov. 16 Tr. at 169:6–10], the '956 patent does not reference screening, but instead merely states that the HB-MSCs should have a certain threshold of IL-6 as compared to BM-MSCs, [TX 2 at 88:28–32 ("[MSCs] in a resting state, express mRNA encoding interleukin-6 at a level which is less than ten percent of the IL-6 mRNA level expressed by [MSCs], in a resting state, derived from bone marrow or adipose tissue . . . .")].

F.3d at 1264, the Court finds that Dr. Wang was not a joint inventor on the ’956 patent. See Eli Lilly, 376 F.3d at 1362 (“A contribution of information in the prior art cannot give rise to joint inventorship because it is not a contribution to conception.”); Dana-Farber Cancer Inst., 964 F.3d at 1372 (“[S]imply informing another about the state of the prior art does not make one a joint inventor.”). Accordingly, Dr. Wang has not provided clear and convincing evidence of significant contributions to the ’956 patent and will not be added to the patent as a joint inventor. See Ethicon, 135 F.3d at 1460–61; Israel Bio-Eng’g Project, 475 F.3d at 1263–64. Judgment for Astellas shall therefore enter on Defendants’ Counterclaim Count I.

2. The ’321 Patent

Drs. Wang and Xu allege that they made several significant contributions to the ’321 patent and should be added to the patent as joint inventors. [ECF No. 221 ¶¶ 113–18]. Their alleged contributions include the idea of comparing HB-MSCs to BM-MSCs (Claims 21, 22), and of mitotically inactivating the HB-MSCs (Claims 17, 18). [Id.]; see [TX 1 (’321 patent)]. Again, the Court has already found that this information was known in the field and by Drs. Kimbrel and Lanza prior to their collaboration with Drs. Wang and Xu, see supra, Section III.E.1, 4, therefore Drs. Wang and Xu contributed, if anything, only well-known concepts, see Israel Bio-Eng’g Project, 475 F.3d at 1263–64; Dana-Farber Cancer Inst., 964 F.3d at 1372. Accordingly, Drs. Wang and Xu have not provided clear and convincing evidence of significant contributions to the ’321 patent and will not be added to the patent as joint inventors. See Ethicon, 135 F.3d at 1460–61; Israel Bio-Eng’g Project, 475 F.3d at 1263–64. Judgment for Astellas shall therefore enter on Defendants’ Counterclaim Count II.

3. The ’551 Patent

As noted earlier, in its Order on summary judgment the Court found that Drs. Kimbrel and Lanza should be named as joint inventors on the ’551 patent. [ECF No. 163]. Astellas now argues that Drs. Wang and Xu did not make inventive contributions to the ’551 patent and asks that they be removed as joint inventors. [ECF No. 219 ¶ 2]. Defendants contend that Drs. Wang and Xu did make significant contributions to the ’551 patent and should remain on the patent as co-inventors with Drs. Kimbrel and Lanza. [ECF No. 221 ¶¶ 103–04].

Defendants assert that they contributed the concepts of mitotic inactivation and IL-6 screening to the ’551 patent, [ECF No. 247-1 ¶¶ 165, 176, 180], but the Court has already determined that these were not inventive contributions. Defendants also focus on their alleged contribution of requiring the use of a GSK3 inhibitor at a particular concentration as being inventive. [ECF No. 221 ¶¶ 103–11; ECF No. 247-1 ¶ 165]. As the Court noted supra, Section III.E.5, the use of GSK3 at the concentrations disclosed and for the purposes discussed in the ’551 patent had already been described in Dr. Brivanlou’s publications, including his patent, and were known to Drs. Kimbrel and Lanza prior to their collaboration with Drs. Wang and Xu.

Defendants first claim that the patent examiner considered their required use of a GSK3 inhibitor at a specific concentration range as rendering the invention novel. [ECF No. 247-1 ¶¶ 170, 173; Nov. 12 Tr. at 154:9–13]. As discussed supra, Section III.H, however, the patent examiner did not conduct a thorough search of prior art and therefore did not identify the Brivanlou publications that disclosed the benefits of using a GSK3 inhibitor and suggested concentration ranges. As to Defendants’ claim that the concentration range (0.05 to 0.2 µm) cited in the ’551 patent was inventive, [TX A], this was within the range disclosed by Dr. Brivanlou’s patent (0.001 to 100 µm, with a stated preference for a range of 0.1 to 1µm),

[TX 33; Nov. 5 Tr. at 59:17–20], and was therefore not inventive. See In re Peterson, 315 F.3d 1325, 1329 (Fed. Cir. 2003) ("In cases involving overlapping ranges, we and our predecessor court have consistently held that even a slight overlap in range establishes a prima facie case of obviousness."); In re Geisler, 116 F.3d 1465, 1471 (Fed. Cir. 1997) (affirming finding of obviousness where range in patent, 100–600, overlapped with range of 50–100 disclosed in prior art). Further, Dr. Brivanlou's publications disclosed the "critical" need to find "a minimal concentration of BIO," [TX 34], which is consistent with Dr. Wang's experimentation and the low range identified in the '551 patent.

Defendants next claim that Dr. Wang chose to use a GSK3 inhibitor for an inventive purpose, namely, to improve the downstream characteristics of the HB-MSCs. [ECF No. 247-1 ¶ 167; Nov. 12 Tr. at 42:15–25]. As discussed supra, Section III.E.5, however, Dr. Wang consistently testified that he used a GSK3 inhibitor to improve EB formation, which—as is clear from Dr. Wang's own contemporaneous documents—was disclosed in Dr. Brivanlou's prior art. [Nov. 9 Tr. at 56:17–22, 64:9–11, 64:19–65:3, 66:11–17, 198:2–8; TX W (Dr. Wang's 2011 PowerPoint presentation, citing Dr. Brivanlou's prior art)]. To be considered joint inventors, Drs. Wang and Xu would have needed to "do more than merely explain to the real inventors well-known concepts and/or the current state of the art" regarding the use of GSK3 inhibitors. Israel Bio-Eng'g Project, 475 F.3d at 1264.

Accordingly, the Court finds that Drs. Wang and Xu did not make significant contributions to the '551 patent and should be removed as inventors. In addition, because the parties stipulated that inventorship on the '122 patent will be aligned to match the Court's determination on inventorship for the '551 patent, Drs. Kimbrel and Lanza should be named as the joint inventors on that patent and Drs. Wang and Xu should be removed as inventors. [ECF

No. 95; ECF No. 218 at 3 n.2; ECF No. 220 at 16; ECF No. 218-1 ¶¶ 37–38]. Judgment for Astellas shall therefore enter on Count I.

B. Count V: Chapter 93A

Astellas seeks damages in connection with its claim that Defendants engaged in unfair and deceptive practices in violation of Section 11 of Chapter 93A by misappropriating its technology and using it for commercial gain. [ECF No. 243 ¶ 88]. Defendants argue that they did not engage in unfair or deceptive acts. [ECF No. 247-1 ¶¶ 226–63].[20]

Chapter 93A creates a private cause of action against those who engage in "[u]nfair methods of competition and unfair or deceptive acts or practices in the conduct of any trade or commerce . . . ." Mass. Gen. Laws ch. 93A, § 2(a). Section 11 allows a plaintiff to seek damages or injunctive relief against a defendant who has engaged in unfair or deceptive acts in violation of § 2, and requires a plaintiff to

> establish (1) that the defendant engaged in an unfair method of competition or committed an unfair or deceptive act or practice, as defined by G. L. c. 93A, § 2, or the regulations promulgated thereunder; (2) a loss of money or property suffered as

[20] Defendants also assert that the statute of limitations and the doctrine of unclean hands bar Astellas' claim. [ECF No. 247-1 ¶¶ 228, 234]. In addition, in their post-trial briefings, Defendants argue for the first time that they were not engaged in trade or commerce for the purposes of Chapter 93A liability. [Id. ¶¶ 240, 244, 249]; see Kraft Power Corp. v. Merrill, 981 N.E.2d 671, 683 (Mass. 2013) ("The addition of § 11" extended Chapter 93A's "protections . . . to persons engaged in trade or commerce in business transactions with other persons also engaged in trade or commerce." (alterations in original) (quoting Manning v. Zuckerman, 444 N.E.2d 1262, 1264–65 (Mass. 1983))). Because the Court finds that Defendants did not engage in unfair or deceptive acts or practices, it will forgo an analysis of these additional arguments and affirmative defenses.

> a result; and (3) a causal connection between the loss suffered and the defendant's unfair or deceptive method, act, or practice.

Auto Flat Car Crushers, Inc. v. Hanover Ins. Co., 17 N.E.3d 1066, 1074–75 (Mass. 2014).

"An act or practice is 'unfair' if it is 'within at least the penumbra of some common-law, statutory or other established concept of unfairness,' is 'immoral, unethical, oppressive, or unscrupulous,' and 'causes substantial injury to consumers (or competitors or other businessmen).'" Blue Cross & Blue Shield v. AstraZeneca Pharm. LP (In re Pharm. Indus. Average Wholesale Price Litig.), 582 F.3d 156, 184 (1st Cir. 2009) (quoting Mass. Eye & Ear Infirmary v. QLT Phototherapeutics, Inc., 552 F.3d 47, 69 (1st Cir. 2009)). "The 'crucial factors' in an unfairness inquiry are 'the *nature* of [the] challenged conduct and on the *purpose* and *effect* of that conduct.'" Id. at 184–85 (alteration in original) (emphasis added) (quoting Mass. Emps. Ins. Exch. v. Propac-Mass, Inc., 648 N.E.2d 435, 438 (Mass. 1995)). "Chapter 93A does not attach liability for all of the unseemly business practices justly loathed by consumers and business professionals. Instead . . . 'the defendant's conduct must be not only wrong, but also egregiously wrong.'" Id. at 185 (quoting Mass. Sch. of Law at Andover, Inc. v. Am. Bar Ass'n, 142 F.3d 26, 41 (1st Cir. 1998)). "Of additional note, 'Chapter 93A liability is decided case-by-case, and Massachusetts courts have consistently emphasized the "fact-specific nature of the inquiry."'" Tomasella v. Nestlé USA, Inc., 962 F.3d 60, 71 (1st Cir. 2020) (quoting Arthur D. Little, Inc. v. Dooyang Corp., 147 F.3d 47, 55 (1st Cir. 1998)).

As to the *nature* and *purpose* of the challenged conduct, Blue Cross & Blue Shield, 582 F.3d at 185, Dr. Xu had not conducted research in partnership with a pharmaceutical company prior to his collaboration with Astellas. While Astellas' witnesses provided testimony about the norms of such collaborations, it was clear from Drs. Wang and Xu's testimony that they were not aware of these norms at the time of the collaboration. Rather than simply test Astellas' HB-MSC

cells as Astellas requested, Drs. Wang and Xu believed they could make improvements and use those cells to further their own research interests. For example, Dr. Wang jumped ahead to modify the protocol in an effort to prepare the cells for commercialization, apparently not knowing that, as demonstrated at trial, the modifications he made were already known in the art and to Drs. Kimbrel and Lanza as being necessary for commercialization. Essentially, Drs. Wang and Xu misunderstood the role Astellas was asking them to play. Further, as the Court has found, Defendants also misunderstood the value of their contributions, leading them to believe they needed to protect those contributions and that Astellas was not adequately compensating them for their efforts. The Court credits testimony from Drs. Wang and Xu regarding the perceived value of their contributions even though the Court finds that they were not, after all, as valuable as they believed.

With regard to the *effect* of Defendants' conduct, Blue Cross & Blue Shield, 582 F.3d at 185, they did disclose the Astellas protocol to one ImStem investor and to the PTO prior to July 18, 2013, when Astellas' application for its '321 patent, which disclosed the protocol, was published. Defendants' '551 patent, which also disclosed the protocol, was not published until July 23, 2015—well after Astellas had publicly disclosed the information. In addition, neither party has a product on the market that uses the HB-MSC technology, therefore Astellas was unable to demonstrate lost sales in connection with Defendants' conduct. Although evidence showed that Drs. Wang and Xu utilized Astellas' technology to begin work on their own T-MSC technology—including through securing grants and investors—Astellas was unable to demonstrate concrete or lasting effects from Defendants' actions. For example, Astellas was unable to identify precisely how the use of the protocol benefitted Defendants' T-MSC development, or how much time, if any, knowledge of the protocol saved in that development.

As a result, while Defendants' actions were wrong, given the Court's conclusions as to Chapter 93A's "critical" purpose and effect factors, the Court cannot find that Defendants' actions were egregiously wrong for purposes of Chapter 93A liability. See Blue Cross & Blue Shield, 582 F.3d at 185. For these reasons, the Court finds that Defendants were not engaged in unfair or deceptive practices as contemplated by Chapter 93A and that Astellas has therefore failed to carry its burden to support a claim under Chapter 93A, § 11. Judgment for Defendants shall therefore enter on Count V.

V. CONCLUSION

Accordingly, for the reasons discussed herein, Dr. Wang will not be added to Astellas' '321 or '956 patents and Dr. Xu will not be added to the '321 patent because they did not make inventive contributions to the patents. In addition, Drs. Wang and Xu will be removed from the '551 patent for failing to make inventive contributions to that patent, and, by stipulation, the '122 patent will be amended to conform with this determination. Lastly, Astellas has failed to show that Defendants violated Chapter 93A. Judgment shall therefore enter for Astellas on Count I and Counterclaim Counts I and II. Judgment shall enter for Defendants on Count V.

SO ORDERED.

February 5, 2021

/s/ Allison D. Burroughs
ALLISON D. BURROUGHS
U.S. DISTRICT JUDGE